REMARKS/ARGUMENTS

Claims 1, 10, 11, and 23-25 are canceled in this amendment without prejudice to prosecution of the subject matter of these claims in continuation or divisional applications. Claims 26, 27 and 85-93 are pending in the application.

Claims 26, 27 and 90 have been amended to recite that the claimed method is a method for reducing proliferation or migration of smooth muscle cells. These amendments to Claims 26, 27 and 90 find support, for example, in the specification at page 6, lines 11-13 (discussing a method for controlling excessive proliferation or migration of smooth muscle cells) and page 13, lines 10-14 (line 11 in particular, which notes that control includes reduction of an unwanted event), and elsewhere in the specification and claims as filed.

Claims 26, 27 and 90 have also been amended to recite that the antagonist antibody binds with high affinity to a native ErbB4 receptor of SEQ ID NO:2. These amendments to Claims 26, 27 and 90 find support, for example, in the specification at page 9, line 21 to page 10, line 5; page 17, lines 14-16; page 42, line 18 to page 43, line 2; page 43 line 18 to page 45, line 12; and elsewhere in the specification and claims as filed.

No new matter is added by way of the amendments to the claims.

Claims 1, 10-11, 23-27 and 85-93 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of inhibiting proliferation or migration of smooth muscle cells *in vitro* comprising administering an effective amount of antibody to native ErbB4 receptor, the Examiner citing the reasoning presented in the Office Actions of March 9, 2004 and September 9, 2004.

Claims 1, 10, 11, and 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681, for the reasons set forth in the previous Office Action mailed September 9, 2004.

Applicants respectfully traverse the rejections with regard to all rejected claims.

Information Disclosure Statements

In the Remarks below, Applicants refer to three references that have not previously been cited. Accordingly, Applicants submit an Information Disclosure Statement (IDS) listing these references.

Upon review of our files, it appears that the IDS filed on July 23, 2002 has not been initialed by the Examiner. Applicants request that the Examiner review the file and, if Applicants belief is correct, Applicants request that the Examiner review the references cited therein and initial the IDS accordingly.

The Rejections of Claims 1, 10-11, 23-27 and 85-89 Under U.S.C. §112, First Paragraph

Claims 1, 10-11, 23-27 and 85-93 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of inhibiting proliferation or migration of smooth muscle cells *in vivo,* comprising administering an effective amount of antibody to native ErbB4 receptor. Claims 1, 10, 11, and 23-25 being canceled in this amendment without prejudice to prosecution of their subject matter in subsequence continuation or divisional applications, the rejections, although traversed, are believed to be moot as to these claims.

Applicants acknowledge the Examiner's statement that the specification is "enabling for *in vitro* method of partially inhibiting proliferation or migration of vascular smooth muscle cells in cell culture." Applicants submit that the specification is also enabling for reducing proliferation or migration of smooth muscle cells comprising treating said smooth muscle cells with an effective amount of an antagonist antibody that binds with high affinity to a native ErbB4 receptor of SEQ ID NO:2 (see, for example, page 55, line 14 to page 62, line 11).

The Rejections Regarding the Claim Term "Inhibiting"

The Examiner notes that "total inhibition of proliferation and migration of smooth muscle cells ... was never achieved ... " (page 3, lines 31-33, Office Action mailed March 1, 2005), apparently interpreting the claim language referring to methods for inhibiting proliferation or migration of smooth muscle cells to include methods for totally

inhibiting proliferation or migration of smooth muscle cells.

The amended claims are directed to methods for reducing proliferation or migration of smooth muscle cells. It is believed that the term "reducing" would address the Examiner's concerns as being directed to lessening the amount of proliferation or migration of smooth muscle cells. Accordingly, Applicants submit that the Examiner's objections regarding alleged lack of support in the specification for "complete inhibition" of smooth muscle proliferation or migration is overcome.

The Rejections Regarding *in vivo* Enablement

It is well established that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims, see, *e.g.*, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). It is also well established that if the art is such that a particular model is recognized as correlating to a specific condition, then reasonable correlation will be accepted, unless the Examiner provides evidence that such correlation does not exist. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). A rigorous or an invariable exact correlation is not a requirement. Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985).

The Federal Circuit has cited the United States Court of Customs and Patent Appeals' statement that "[A] specification disclosure which contains a teaching in the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of S. 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)" cited in In re Brana, 51 F.3d 1560, 1566.

Applicants respectfully submit that an Examiner must provide a reasonable explanation as to why the scope of the protection provided by a claims is not

adequately enabled by the disclosure (In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); M.P.E.P. §2164.04):

> "it is incumbent upon the Patent Office ... to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. " In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370.

Similarly, the M.P.E.P. at §2164.04 notes that "[a]ccording to *In re Bowen*, 492 F.2d 859,862-3, 181 USPQ 48, 51 (CCPA 1971), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement." Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Although the Examiner has acknowledged that the specification is enabling for an *in vitro* method of partially inhibiting proliferation or migration of vascular smooth muscle cells in cell culture, the Examiner suggests that "it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of an effective amount of antibody to native Erbb4 receptor will reduce cell proliferation as was monitor [sic] by decreasing in the uptake of BrdU into said cell(Example 2) and reduce migration (Example 3) accurately reflects the relative mammal efficacy of the claimed therapeutic strategy" (Office Action dated 3/01/05, page 3, lines 5-9). The Examiner goes on to say that "The specification does not teach how to extrapolate data obtained from an *in vitro* assay studies to the development of effective *in vivo* mammalian therapeutic treatment, commensurate in scope with the claimed invention" (Office Action dated 3/01/05, page 3, lines 11-13).

A mere assertion by the Examiner that "since no animals were used ... it is not clear that ... culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native ErbB4 receptor will reduce cell proliferation" (page 3, lines 3-7, Office Action mailed March 1, 2005) does not meet the Examiner's burden to provide evidence that the in vitro model does not correlate with the claimed invention (MPEP 2164.02, Working Example), nor does such an assertion provide acceptable evidence or reasoning which is inconsistent with the contested statements. The initial

burden is on the Examiner to give reasons for a lack of enablement and for lack of correlation of an in vitro model in the examples (M.P.E.P. §2164.02). As a result of failing to meet such burden, Applicants submit that the rejection is improper and should be withdrawn.

Applicants note that the Court of Customs and Patent Appeals stated (when discussing the utility of an invention) that "No authority has been cited and we have been able to find none which requires that in order to secure a patent, utility of a pharmacologically active substance must be proved by in vivo testing." In re Isaacs and Lindenmann, 146 USPQ 193, 195 (1965).

In particular, Applicants note that *in vitro* data may support claims to *in vivo* methods (see, *e.g.,* In re Brana, 51 F.3d 1560, 1561, 34 USPQ2d 1436,1441 (Fed. Cir. 1995, as cited at M.P.E.P. §2164.01(a)). The legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in Cross v. Iizuka, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. §2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described. As discussed above, one of ordinary skill in the art would understand and accept that the specification teaches that an effective amount of antibody to native Erbb4 receptor will reduce smooth muscle cell proliferation and that such treatment would be effective *in vivo.*

There is a Nexus Between the in vitro Models and in vivo Efficacy

In addition, it is well accepted in the art that *in vitro* data supports claims of *in vitro* applicability. Moreover, Applicants submit that one of ordinary skill in the art, presented with the teaching of the specification, would understand and accept that the *in vitro* data makes clear that an effective amount of antibody to native Erbb4 receptor will reduce cell proliferation, and would understand and accept that this demonstration teaches that such treatment would be effective *in vivo*.

In vitro assays of smooth muscle cell proliferation and migration were well known at the time the application was filed, and were accepted as relevant to clinical questions. For example, such assays were used to study vascular smooth muscle cell proliferation (Wakino *et al.,* "Retinoids Inhibit Proliferation of Human Coronary Smooth Muscle Cells by Modulating Cell Cycle Regulators," *Arterioscler Thromb Vasc Biol* **21**:746-751 (2001) and endothelial cell migration in response to mechanical injury (*e.g.,* Lauder *et al.,* "Quantification of the repair process involved in the repair of a cell monolayer using an *in vitro* model of mechanical injury," *Angiogenesis* **2(1)**:67-80 (1998). Applicants note, for example, that Poon *et al.,* "Rapamycin Inhibits Smooth Muscle Cell Migration," *J. Clin. Invest.* **98**:2277-2283 (1996), based on their *in vitro* results, followed up with further *in vitro* and also *in vivo* experiments, which results were published in a clinical journal.

In addition, an *in vitro* study of smooth muscle published at about the time of filing of the present application concluded that "phytoestrogens are powerful antioxidants able to interfere with AGEs-mediated oxidative DNA damage of VSMC, and are potentially useful against vascular diseases where ROS are involved in hypertension" (page 1839, Mizutani *et al.*, *Journal of Hypertension* **18**:1833-1840 (2000)). An *in vitro* study of collagen effects on smooth muscle cell migration concluded with the following: "These studies suggest that type VIII collagen plays a critical role in regulating SMC invasion and migration after vascular injury" (page 475, Hou *et al.*, *American Journal of Pathology* **1562**: 467-476 (2000)). Similarly, an *in vitro* study of human aortic smooth muscle cells concluded that "[a]gents that cause accumulation of cAMP may be considered as antiproliferative drugs against VSMC

proliferation" (page 242, Hayashi *et al.*, *Hypertension* **35(2)**:237-243 (2000), where VSMC stands for vascular smooth muscle cell).

Thus, the conclusion of Hayashi *et al.* that analogues of cAMP having direct inhibitory effects on VSMC proliferation can be considered potential antiproliferative drugs against VSMC growth (see Abstract and Discussion sections, Hayashi *et al.*, *Hypertension* 35:237 (2000) cited above); the conclusion of Hou *et al.* that type VIII collagen plays a critical role in regulating SMC invasion and migration *in vivo* - *i.e.,* after vascular injury (Hou *et al.*, *American Journal of Pathology* 156:467 (2000) cited above) and the conclusion of Mizutani *et al.* that phytoestrogens interfere with advanced glycation end-products-mediated oxidative DNA damage of vascular smooth muscle cells and are therefore potentially useful in vivo, *i.e.,* in vascular disease involving reactive oxygen species (Mizutani *et al.*, *Journal of Hypertension* 18:12 (2000) cited above) are all consistent with the Applicants' submission that the present specification supports both *in vivo* and *in vitro* claims.

Thus, such *in vitro* assay results as disclosed in the present application would have been recognized in the art at the priority date as indicative of similar applicability *in vivo*. This sampling of the scientific literature regarding smooth muscle cell proliferation published at about the time of filing of the present application demonstrates that one of ordinary skill in the art at the time would have reasonably believed that compounds and treatments shown to be effective on smooth muscle cell migration and proliferation *in vitro* would also be effective *in vivo*.

As was discussed above, Applicants submit that the Examiner's mere suggestion that "it is not clear that reliance on the *in vitro* data ... will reduce cell proliferation" does not provide a reasonable explanation as to why the scope of protection provided by the claims is not adequately enabled by the disclosure, and so fails to meet the burden required by statute and case law to rebut the enablement of the disclosure (In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); M.P.E.P. §2164.04). Moreover, in the present case, even if the Examiner had met the burden (which he has not), Applicants have overcome the rejection by providing *in vitro* data for the claimed

methods of inhibiting proliferation or migration of smooth muscle cells, using art recognized assays recognized as correlating with *in vivo* results. As discussed above, one of ordinary skill in the art reading the written description contained in the specification, and based on the art-recognized assays and art-recognized correlation between *in vitro* data and *in vivo* activity, would have recognized that Applicants have enabled the claimed invention.

The Specification Provides Support for the Claimed Invention

Applicants note that the specification teaches how to make and use the invention (*e.g.,* on pages 55-62). The specification presents data showing reduced proliferation (Example, 2, pages 67-68) and showing reduced migration (Example 3, pages 68-69) as a result of treatment with novel antibody antagonists (*e.g.,* novel immunoadhesins) useful for the claimed methods. These data indicate that the novel immunoadhesins of the examples are able to inhibit proliferation and migration of smooth muscle cells as claimed. The specification thus provides support for the scope of the protection provided by a claims, which Applicants submit are adequately enabled by the disclosure. For example, the specification teaches and provides examples regarding the claimed therapeutic compositions and novel methods and disease conditions susceptible of treatment by them (see, *e.g.,* pages 55-62), including explicit dosage ranges (page 62); methods for identifying molecules that affect proliferation or migration of smooth muscle cells (see, *e.g.,* pages 62-65); methods for making the novel immunoadhesins disclosed in the specification (see, *e.g.,* pages 65-67); effects of the novel immunoadhesins on human aortic smooth muscle proliferation (see, *e.g.,* 67- 68); and effects of the novel immunoadhesins on human aortic smooth muscle migration (see, *e.g.,* 68-69). Thus, notwithstanding the Examiner's characterization of the disclosure of pages 55-62 as "prophetic," the specification includes disclosure that teaches one of ordinary skill in the art how to practice the claimed invention.

Applicants note that the specification teaches amounts and methods of the disclosed pharmacological agents that may be used to practice the invention (see, *e.g.,* the *in vitro* examples, such as at page 67, line 25; page 68, line 16; and Table 3,

page 71-72, and page 72, line 15). The Federal Circuit, discussing utility, stated that "there is reasonable correlation between the disclosed *in vitro* utility and *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." Cross v. Iizuka, 752 F.2d 1040,1050 (Fed. Cir. 1985). As noted above, the specification provides disclosure of pharmacological activity of the novel compositions in *in vitro* models of diseases based on cultures of the human cells affected in the target disease conditions.

Accordingly, Applicants respectfully submit that the claim rejections under 35 U.S.C. §112, first paragraph, and in particular the rejections of Claims 26, 27 and 85-93 as allegedly not described in the specification in such a way as to be enabling is overcome. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection and allow the claims.

The Rejections of Claims 1, 10, 11, and 23-26 Under 35 U.S.C. §103(a)

Claims 1, 10, 11, 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,811,098 (Plowman) in view of Krymskaya (1999) or WO 99/02681 (Godowski), for the reasons set forth in the previous Office Action mailed March 9, 2004. Claims 1, 10, 11, and 23-25 being canceled in this amendment without prejudice to prosecution of their subject matter in subsequence continuation or divisional applications, the rejections are believed to be moot as to these claims. Accordingly, although the rejections to Claims 1, 10, 11, and 23-25 under 35 U.S.C. §103(a) are traversed, only the rejection to Claim 26 will be addressed in the following discussion.

In order to establish a *prima facie* case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art,

and not based on the Applicants' disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The requirement that an Examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. The motivation to modify a reference can come from: (1) the nature of the problem to be solved, (2) the teachings of the prior art itself, or (3) the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d at 1358; 47 U.S.P.Q.2d at 1458.

Applicants submit that the Examiner has failed to establish a *prima facie* case that the claimed invention is obvious over the cited references.

For the sake of brevity, Applicants hereby incorporate by reference the remarks and arguments presented in prior responses regarding the rejections of the claimed inventions as allegedly being obvious over Plowman (U.S. Patent No. 5,811,098) in view of Krymskaya or Godowski (WO 99/02681). Applicants note, however, that Applicants' prior remarks and arguments include noting (as was also stated by the Examiner) that Plowman is directed to cancer cells, does not disclose nor suggest a method for controlling excessive proliferation or migration of smooth muscle cells. Moreover, Applicants noted that Godowski does not suggest that antagonists to ErbB4 receptors might be useful to control smooth muscle proliferation; and that Krymskaya teaches that ErbB4 receptors are inactive on airway smooth muscle cells.

Further with regard to Plowman, and contrary to the Examiner's suggestion on page 5 of the Office Action dated March 1, 2005, the '098 patent disclosure of a method of controlling proliferation of cancer cells by antagonizing HER4 receptor would not render obvious controlling proliferation of vascular smooth muscle cells.

In addition and contrary to the Examiner's statement on page 6 of the Office Action, Applicants' recited antibody, an antibody that binds the same epitope as an antibody produced by the deposited hybridomas, is patentably distinct from the anti-HER4 (anti-ErbB4) antibodies of the '098 patent because Applicants' hybridomas and the antibodies they produce are uniquely disclosed in Applicants' specification.

Applicants note that Plowman nowhere cites the hybridomas recited in the claims of the present application.

Similarly, the WO99/02681 reference does not disclose Applicants' claimed ErbB4 antagonist antibody which binds the same epitope as an antibody produced by Applicants' deposited hybridomas.

The Krymskaya et al. reference discusses expression of ErbB4 in human airway smooth muscle cells (HASM cells) and further discusses that EGF activated ErbB2 and EGFR but not ErbB3 or ErbB4. In view of Krymskaya's demonstration that ErbB3 and ErbB4 have no effect there can be no motivation to include the Krymskaya et al. reference in the combined references because its demonstration of the lack of ErbB4 activity in smooth muscle cells teaches away from the claimed invention. Krymskaya provides no disclosure nor even any suggestion to antagonize the activity of the ErbB4 receptor for any reason, much less to inhibit proliferation or migration of smooth muscle cells. As a result, there is no suggestion to use the claimed antagonist antibody for that purpose.

Because of the deficiencies of each of the cited references, there is no motivation to combine them and the Examiner has made no prima facie showing of obviousness. Even if the references were to be combined (which they should not be), the combination does not yield Applicants' claimed invention of a method of using the recited ErbB4 antagonist antibody to reduce proliferation or migration of vascular smooth muscle cells for at least the reason that the combined references fail to disclose the claimed antibodies and fail to disclose the use of the claimed antibodies in methods for reducing reduce proliferation or migration of vascular smooth muscle cells.

Applicants acknowledge the Examiner's statement that "unobviousness cannot be established by attacking the references individually when the rejection is based upon the combination of the references" (page 5, lines 8-10, citing In re Keller and In re Young). As in previous responses, in the present response applicants address the failure of the *combined* references to make obvious the claimed invention. As noted in previous responses, Applicants submit that there is no motivation in the references or in the art to combine the references, nor do the cited references provide a reasonable

expectation of success for such a combination were it to be made. In addition, applicants submit that an assertion that it may be "obvious to try" a course of action or method is not a proper nor sufficient basis for an obviousness rejection. Each of these issues is addressed in the following discussion.

There is no Motivation to Combine the Cited References

Applicants submit that there is no motivation in the references or in the art to combine the references. For example, Plowman is directed to cancer cells, not smooth muscle cells; Godowski, although mentioning that smooth muscle cells are among the cell types that may have ErbB4 receptors, does not discuss proliferation or migration of smooth muscle cells; and Krymskaya teaches that "... in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB4 are functionally inactive" (page L252, column 2, lines 7-9) and "ErbB-3 and ErbB4 in EGF-stimulated cells did not appear to be activated" (page L248, column 2, lines 37-39). Thus, there is no motivation to apply Plowman to smooth muscle cell proliferation or migration, Plowman being directed to cancer cells and not smooth muscle. Godowski, not discussing proliferation or migration of smooth muscle cells, provides no suggestion or motivation to be combined with other references with respect to proliferation or migration of smooth muscle cells. Krymskaya, teaching that ErbB4 receptors are inactive on smooth muscle cells provides no motivation or suggestion to be combined with other references in order to affect proliferation or migration of smooth muscle cells. Thus, the cited references do not provide any motivation of suggestion to be combined in an attempt to provide the claimed methods directed toward reducing proliferation or migration of smooth muscle cells utilizing an antibody antagonist that binds with high affinity to a native ErbB4 receptor of SEQ ID NO: 2.

In addition, Applicants note that the Federal Circuit has stated that "[O]bvious to try is not the standard" (Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000)) and that "[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103." (Gillette Co. v. S. C. Johnson & Son, Inc., 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997)). Thus,

the mere mention of an element of the claimed invention, without more, does not make the claimed invention obvious.

Even if combined, these references taken together fail to provide the claimed invention. The cited references mention: *i)* that ErbB4 receptors may be present on smooth muscle cells (Godowski, Krymskaya), *ii)* that there may be antibodies to such receptors (Plowman, Godowski), and *iii)* that such receptors are inactive in airway smooth muscle (Krymskaya). Combining these suggestions, we find that inactive ErbB4 receptors may be present on smooth muscle cells, and that antibodies to such inactive ErbB4 receptors may be made.

However, the combined references fail to provide any suggestion that ErbB4 receptors might play a role in smooth muscle proliferation or migration, or that such a (non-existent) role could be antagonized, or that antibodies to ErbB4 receptors may have an effect on smooth muscle proliferation or migration.

Applicants note that the antibodies recited in the method of Claim 26 bind the epitope that is bound by the antibody produced by one of the named, novel hybridoma cells. Such antibodies, hybridomas, and epitopes for which the novel antibodies from the novel hybridomas compete for binding are nowhere disclosed, and nowhere suggested, by any combination of the cited references. Accordingly, Applicants submit that, for this reason at least, in addition to the other reasons previously discussed, Claim 26 is not made obvious by any combination of the cited references.

The combined references do not provide any suggestion that an antibody antagonist of a native ErbB4 receptor could be used to treat a smooth muscle cell effective to inhibit proliferation or migration of a smooth muscle cell. Moreover, the disclosure by Krymskaya that such ErbB4 receptors are inactive on human airway smooth muscle cells teaches away from the present invention. As a result, the combined references suggest that there cannot be *an effective amount* of such an antibody antagonist. Thus, the combination of the cited references fails to provide at least several of the required elements of the claimed invention of Claim 26, the combined references also fails to make Claim 26 obvious.

The Combination of the Cited References Does Not Provide a Reasonable Expectation of Success for the Claimed Invention

As was also discussed previously, for at least the reasons discussed above, one of ordinary skill in the art would have no reasonable expectation of success even if the references were to be combined. None of the references suggest that ErbB4 receptors are involved with proliferation or migration of smooth muscle cells; in fact, Krymskaya states that ErbB4 receptors are not active in HASM cells. Thus, in view of the teachings of the cited references, one of ordinary skill in the art would not expect an antibody antagonist of a native ErbB4 receptor of SEQ ID NO: 2 to inhibit proliferation or migration of smooth muscle cells. Accordingly, the cited references fail to provide a reasonable expectation of success for the claimed invention.

Accordingly, the cited references failing to provide all the elements of the claimed invention, failing to suggest or provide motivation to provide such elements or to be combined in an attempt to do so, and failing to provide a reasonable expectation of success for such a combination, Applicants submit that the Examiner has failed to provide a *prima facie* case of obviousness.

Moreover, even if the Examiner had provided a *prima facie* case of obviousness under 35 U.S.C. §103, such a case is rebutted by the references cited by the Examiner. As discussed above, Krymskaya explicitly *teaches away* from the claimed invention, stating that ErbB4 receptors in human airway smooth muscle are inactive (Krymskaya, page L248, column 2, lines 37-39 and page L252, column 2, lines 7-9).

Applicants note that the Federal Circuit has stated that "A *prima facie* case of obviousness can be rebutted if the Applicant . . . can show 'that the art in any material respect taught away' from the claimed invention." In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997) (quoting In re Malagri, 499 F.2d 1297, 1303, 182 USPQ 549, 533 (CCPA 1974)). Teaching away has been defined by the Federal Circuit: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant." Tec Air, Inc. v. Denso Mfg. Mich. Inc., 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999). It is clear that Krymskaya, teaching that ErbB4

receptors on HASM are inactive, teaches away from the claimed invention in a material way. It is also clear that one of ordinary skill, reading Krymskaya, would be taught that interactions with ErbB4 receptors would be ineffective for inhibiting proliferation or migration of smooth muscle cells, and thus would be led away from the path taken by the present Applicants.

Accordingly, the Examiner having failed to provide a *prima facie* case of obviousness, and the cited references rebutting such a *prima facie* case if it had been provided, Applicants respectfully submit that the rejections under 35 U.S.C. §103(a) are overcome, and in particular the rejection of claim 26 under 35 U.S.C. §103(a) is overcome.

CONCLUSION

Applicants believe all rejections to be overcome by the amendments and arguments above, and request reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

If any rejections or objections remain, Applicants request that an interview with the Examiner, either in person or via telephone, before the issuance of the next Action in this case to allow discussion of such issues as may remain.

Please charge the fees for extension of time, and any additional fees that may be required, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0072 A2**.

Respectfully submitted,

Date: July 28, 2005

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